A Proteomic Investigation of Alzheimer's Disease

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Background

Alzheimer's Disease (AD) is the most common form of dementia and is characterized by a progressive decline in cognition and everyday function. For decades, AD research has centered around the aggregation of amyloid and tau proteins. Evidence indicates that the biochemical and cellular phases of the disease are not entirely understood. There is a need for a better understanding of the underlying disease processes to allow for early detection and the ability to halt progression through more effective treatment options. Proteomics research is capable of providing much of the missing pieces when it comes to understanding the underlying disease processes of AD.

Recently, Johnson et al. developed a mass spectrometry pipeline utilizing tandem mass tag (TMT) technology which allowed for quantification of proteins in brains from control, asymptomatic, and symptomatic cases of AD.

The goal of this project was to expand upon the data published from Johnson et al. by narrowing in on a comparison between asymptomatic AD and AD protein abundances. The presented findings arising from the computational analysis highlight interesting biological processes that may shed more light into the mechanism leading to disease progression in AD. Further study into these mechanisms in AD can help increase our understanding and lead to an eventual advancement in early intervention and better treatment options for AD.

Image from the National Institute on Aging, NIH

Illustration of the yellow beta-amyloid plaques and the blue neurofibrillary tau tangles that disrupt neuron transmission and lead to neurodegeneration.

Methods

Emory University School of Medicine

- Collection and Preparation of Samples
- TMT Pipeline and Protein Quantification
- Published Public Data

Investigation of Proteomics Data

- Using R Software and R Studio
  - Filtered Data to Significant P-Values
  - Filtered Significant P-Values to Significant P-Values for the Difference of Asymptomatic AD – AD
  - Filtered to Positive and Negative Differences in the P-Values of Asymptomatic AD – AD
  - Created a Volcano Plot to Display Protein Abundance Findings
- Ran a Gene Ontology (GO) Term Analysis of the Significant Proteins

Data Representation

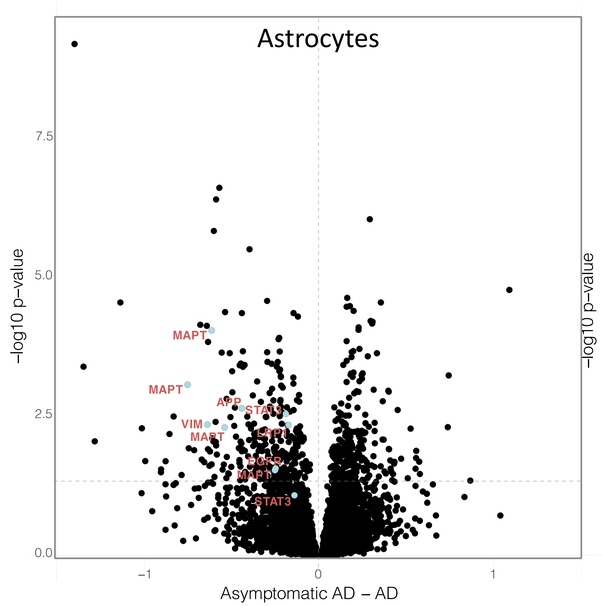


Figure 1. Highlighted proteins are enriched in AD compared to asymptomatic AD and are involved in the activation, development, and differentiation of astrocytes.

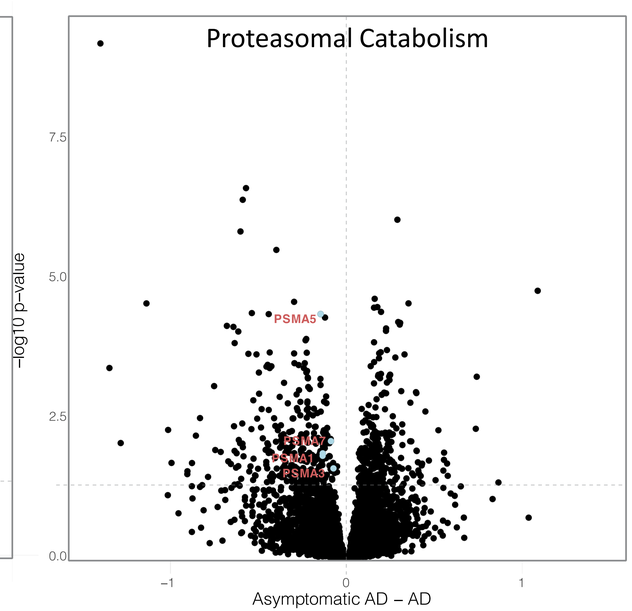


Figure 2. Highlighted proteins are enriched in AD compared to asymptomatic AD and are alpha subunits of the proteasome playing a role in protein catabolism which in this case is ubiquitin-independent.

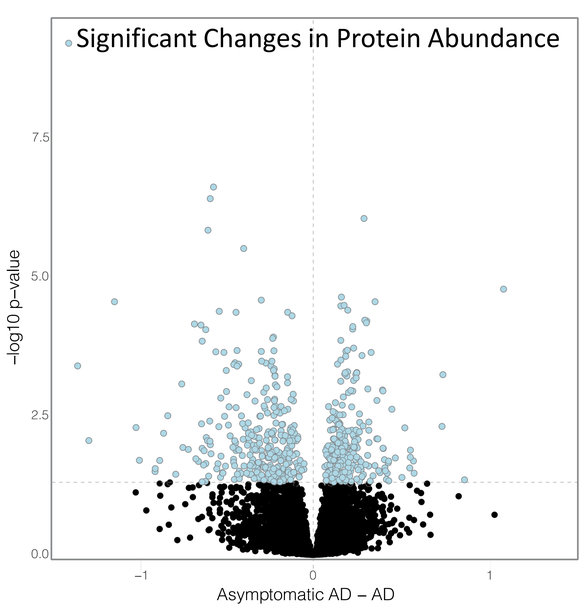


Figure 3. Highlighted proteins are in significant abundance when comparing asymptomatic AD and AD.

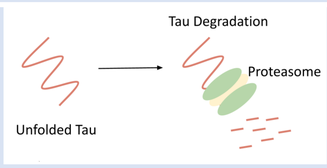
Gene Ontology Analysis

Astrocytes

Image by Kateryna Kon

- Enriched activation, development, and differentiation processes of Astrocytes in AD
- Evidence points to astrocytes as an important biomarker
- Potential biomarker that can successfully diagnose, differentiate, or predict the rate of decline between AD disease stages
- Next Steps: Explore the relationship of astrocyte processes comparing asymptomatic AD and cognitively healthy cases to be able to understand astrocytes as biomarkers for the rate of cognitive decline

Proteasomal Catabolism



- Enriched ubiquitin-independent protein catabolic processes in AD
- Process may be enriched for several reasons
  - Over-compensation in degradation pathways to attempt homeostasis as proteins aggregate in AD
  - Lack of sufficient ubiquitin-dependent protein catabolism
  - Normal tau degradation does not require ubiquitin
- Next Steps: Investigate proteasome interaction in AD to gain insight which may prove helpful in developing treatment options

Conclusion

- Proteomics research allows for a better understanding of the underlying disease process of AD.
- Biological processes related to astrocyte activation, development, and differentiation are enriched in AD compared to asymptomatic AD.
- Ubiquitin-independent protein catabolic processes are also enriched in AD compared to asymptomatic AD.
- Comparing the protein abundance between two stages of the disease provides a way for early intervention methods to be discovered and better treatment options developed.
- Future Step: Incorporate findings comparing between control and asymptomatic data to better understand the underlying disease processes.

Acknowledgments

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References

Johnson, E., Dammer, E., Duong, D., Yin, L., Thambisetty, M., Troncoso, J., Lah, J., Levey, A., & Seyfried, N. (2018). Deep proteomic network analysis of Alzheimer's disease brain reveals alterations in RNA binding proteins and RNA splicing associated with disease. *BioMed Central Journal, 13*(52). https://doi.org/10.1186/s13024-018-0282-4

National Institute on Aging, NIH. (2018, April 10). *How is Alzheimer's Disease Treated?* https://www.nia.nih.gov/health/how- alzheimers-disease-treated

Rayaprolu, S., Higginbotham, L., Bagchi, P., Watson C., Zhang, T., Levey, A., Rangaraju, S., & Seyfried, N. (2020). Systems-based proteomics to resolve the biology of Alzheimer's disease beyond amyloid and tau. *Neuropsychopharmacology Reviews. 46*, 98-115(2021). https://www.nature.com/articles/s41386-020-00840-3

González-Reyes, R., Nava-Mesa, M., Vargas-Sánchez, K., Ariza-Salamanca, D., & Mora-Muñoz, L. Involvement of Astrocytes in Alzheimer's Disease from a Neuroinflammatory and Oxidative Stress Perspective. (2017). *Frontiers in Molecular Neuroscience.* https://doi.org/10.3389/fnmol.2017.00427

Grune, T., Botzen, D., Engels, M., Voss, P., Kaiser, B., Jung, T., Grimm, S., Ermak, G., & Davies, K. (2010). Tau protein degradation is catalyzed by the ATP/ubiquitin-independent 20S proteasome under normal cell conditions. *Archives of Biochemistry and Biophysics, 500*(2), 181-188. https://doi.org/10.1016/j.abb.2010.05.008